

ESSEX FUND PRIZE DISSERTATION. NO. LIV.

VACCINE-THERAPY.

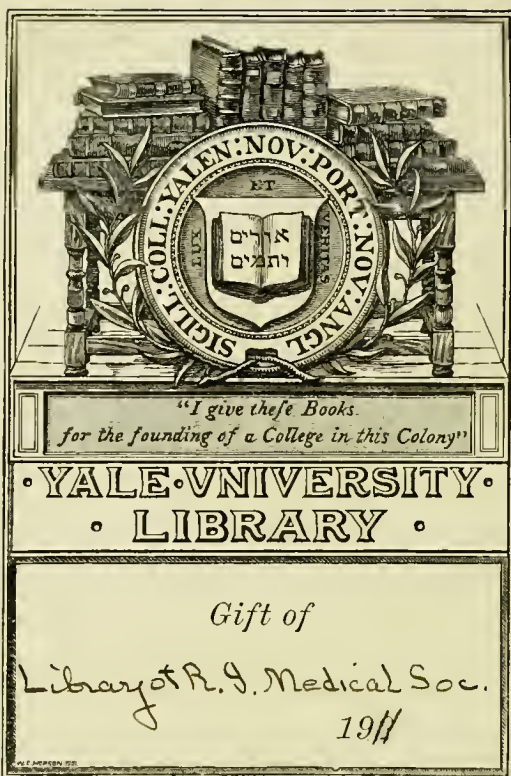
MOTTO:

"Vis Medicatrix Naturæ."

BY

WILLIAM C. OWING, M.D.

PARRIS, N. Y.



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PAWTUCKET, R. I.

PROVIDENCE;

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1911.

THE Trustees of the Fiske Fund, at the annual meeting of the Rhode Island Medical Society, held at Providence, June 1, 1911, announced that they had awarded a premium of two hundred dollars to an essay on "Vaccine-Therapy," bearing the motto:

"Vis Medicatrix Naturae."

The author was found to be WILLIAM G. DWINELL, M. D., of Pawtucket, R. I.

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FOREWORD.

“Contention that, in connexion with every cure which is credited to vaccine-therapy, the possibility of that cure having taken place spontaneously should be taken into consideration, appears at first sight to be a perfectly reasonable contention. When I urge upon you that the *vis medicatrix naturae* comes insistently to the aid of the physician, even where he ignorantly opposes it, and when I ask you to reflect that among all the therapeutic methods which have been practised there is probably not one—be that method never so harmful—which is not credited with many cures, you will perhaps realize that I can have no possible quarrel with the critic who demands that it shall be demonstrated to him, in connexion with the cures which are ascribed to vaccine-therapy, that they are not to be credited to the spontaneous operations of nature.

The critic who makes this demand from me may therefore be assured that he is forcing an already open door. When he contends that spontaneous cures of bacterial disease do occur, he is only emphasizing one of the fundamental axioms upon which the immunisator builds. For if it were not for the fact that spontaneous cures do occur, and for the fact that there follows upon these in many cases a condition of insusceptibility to further infection, the immunisator would have no warranty for expecting anything either from prophylactic or therapeutic inoculations. In other words, were it not that nature is competent to bring about these results under the stimulus of auto-inoculation, assuredly all attempts to bring them about by artificial inoculations would be vain.”—WRIGHT.

VACCINE-THERAPY.

As the prophylaxis and cure of disease are among the most important of those questions which are engrossing the attention of humanity it is natural that very great attention should have been devoted to it from the most remote time. We see primitive races, the ordinary layman, medical men, legislators and even the most subtle thinkers devoting their energies to the solution of the problem of immunity against poisoning, and against infections. Historical science will never reveal to us the earliest sources of our knowledge on this question, so remote are their origins. The wide distribution of several methods for protecting man and cattle against certain diseases clearly proves that the origin of this practice dates from a very early period. The Chinese assert that they have been familiar with the principles dealing with immunization against smallpox since the beginning of the 11th century. According to the account of Timoni, a Greek physician practising in Constantinople in the first half of the 18th century, the Circassians and Georgians, intent upon preserving the beauty of their daughters, made punctures at various points in the skin with needles charged with variolus virus. In 1798 after

twenty years of work Jenner published his first account on the utility of vaccination with virus of cowpox. In 1880 Pasteur prepared two vaccines for prophylactic use, one against anthrax, and one against swine erysipelas. In light of recent knowledge Pasteur's immunity theories were crude but they served a purpose, and attracted the attention of many scientific thinkers. As far back as 1858 Haeckel had observed that particles of indigo injected into the veins of certain molluscs could shortly afterwards be found in the cells of the animal. The significance of this and other observations was not appreciated until Metchnikoff in 1883 called attention to their bearing on infection and immunity. The outcome of his investigations was the establishment of the well known doctrine of phagocytosis.

Metchnikoff believes that susceptibility to or immunity from infection is essentially a matter between the invading bacteria on the one hand, and the leucocytes on the other. He realizes that the serum constituents play an important role, but this role consists in their stimulating the leucocyte to take up the bacteria.

In 1895 Denys and Leclef called attention to the action of blood serum on phagocytosis and they produced reliable experimental evidence that there were present in the blood serum of immunized rabbits substances which alter microbes in such a way as to per-

mit of their ingestion by leucocytes. In 1897 Bordet was unable to confirm their results. Munnies however in the same year demonstrated that the immunity of guinea-pigs inoculated with cultures of pneumococci depends on a modification of their serum whereby an active phagocytosis is induced, and that this was not due to any especial activity of the leucocytes. In 1902 Leishman devised a method of quantitatively estimating the phagocytic power of blood to staphylococci. In 1903 Wright and Douglas introduced the word opsonin (opsono, I prepare the food for) to characterize the substance in normal blood which they believed prepared the microbes for ingestion by the leucocytes. In 1904, Neufeld and Rimpau independently of Wright alluded to the two well known elements in immune serum (i. e. antitoxins and bacteriocidal substances) and stated that they had found a third element which they claimed sensitized the bacteria but did not act on the leucocytes. To Wright and Douglas belong the distinction of making the necessary clinical application of these discoveries which has resulted in the opsonic or vaccine treatment of disease.

OPSONIN. Inasmuch as the foundation of Vaccine Therapy rests upon the action of opsonin it might be well to consider the properties ascribed to this substance. Its existence as a distinct antibody has been fully proven by Hektoen, Rudiger and others in this country, by Wright and Douglas in England and by

Ehrlich, Neufeld, Rimpau and many others on the continent. By absorption experiments *in vitro* the following facts have been elicited :

1. Heat may destroy the opsonic power, or opsonin, of serum leaving the lytic amboceptor intact.

2. Serum, normal or immune may contain opsonin for a given organism, but not, at least as far as is yet known, the proper amboceptor for the organism.

3. A serum may contain opsonin for a bacterium but no agglutinin and the opsonin may persist after the bacteriolytic complement has been destroyed by heat.

4. Hemo-opsonic sera or sera which prepare the red cells for phagocytosis are probably distinct substances, and go far to prove that opsonins are distinct antibodies.

Opsonins are then distinct antibodies: constituents of normal and immune sera. Opsonins are cell receptors, and belong to the second order of receptors as postulated by Ehrlich. They have two groups, a haptophore or binding group which combines with the organism or cell, and an opsoniferous group containing the specific substance.

That the importance of the last paragraph may be fully appreciated I should like to digress a short way from the immediate subject, and call the attention of the reader to a subject closely correlated to the one

under discussion, namely that of the cell concept as taught by Ehrlich.

Virchow in his "Cellular Pathology," expressed the following view: "Just as the single cell of a fungus or an alga abstracts from fluid in which it lives as much and the kind of material as it needs for its vital processes, so also the tissue cell within a compound organism possesses elective properties by virtue of which it disregards certain substances and takes up and utilizes others."

Ehrlich applies the name receptor to this "elective property" of the cell and assumes that the living protoplasm possesses side chains or receptors which possess a maximum chemical affinity for nutritive substances, and that they anchor these substances to the cell. To those receptors which are enabled and designed to assimilate food stuffs for the cell, he gives the name of nutri-receptor. He considers that these nutri-receptors constitute the source of the antibodies.

The cell then receives its food through a bio-chemical reaction called a receptor, and in case the substance so caught up is of a purely nutritive character such as the simple fats or sugars it serves the vital functions of the cell. In case of the toxin molecule the first part of the anchoring process through the receptor is the same as with the fats and the sugars, but instead of being assimilated as was the food particle the toxin molecule occupies the particular receptor which has

attracted it. This receptor is therefore unable longer to anchor nutritive material. The cell has thus suffered a loss which must be replaced.

In such processes it is very common to find, as Weigert's researches have shown, that the loss is not merely replaced, but that it is over-compensated. The same thing takes place in the methodical immunization when continued and ever increased doses of immunizing substances are introduced. Part of the newly formed receptors still attached to the cell are occupied by immunizing substances only to be replaced by a generation greater in degree than before. Owing to this increased demand the protoplasm to a certain extent is trained in one direction, namely, to produce anew a certain kind of constituent, the receptors in question. Finally, such an excess of receptors is produced that there is no longer room in the protoplasm for them. Then they are thrust off as free molecules and pass into the body fluids. Here they present themselves as the antibodies in various forms: agglutinins, precipitins, anboceptors and opsonius and as antitoxins and antiferments.

Opsonin then is an antibody the product of cell physiology. It exerts its protective power by uniting with the bacteria thereby rendering their phagocytosis more easy of accomplishment. Metchnikoff believes there is but one element in immunity innate or acquired and that is phagocytosis. This in the light

of Ehrlich's work holds good only in part for Ehrlich has conclusively shown that the role of the phagocyte in diphtheria and tetanus infection is not entirely a phagocytic one. Metchnikoff's phagocytotic theory may then be restricted perhaps to apply to those bacteria which do not produce extracellular toxins in culture media and against which the economy defends itself by the production of antibodies such as bacterioly-sins, agglutinins, precipitins, opsonins and others while those organisms producing extracellular toxin in culture media are combatted by antitoxins.

The opsonic index is the term used to express the opsonic content of a serum. It is estimated in the following way: An emulsion of fresh human leucocytes is made by dropping twenty drops of blood from a finger prick into 20 c. c. of normal salt solution containing one per cent. sodium citrate. The mixture is centrifuged, the supernatant clear fluid removed and the upper layers of the sedimented blood cells transferred by means of a pipette to 10 c. c. normal salt solution. After centrifuging the second mixture the supernatant fluid is pipetted off and the remaining suspension used for opsonic tests. Such a "leucocyte emulsion" of course contains an enormous number of red blood cells; the proportion of leucocytes, however, is greater than in the original blood. One volume of this emulsion is mixed with one volume of the bacterial suspension to be tested and with one volume of the patient's serum.

All three are now expelled on a slide and thoroughly mixed by drawing back and forth into the pipette. Then the mixture is sucked into the pipette, the end sealed and the whole put into the incubator at 37 degrees C. The identical test is made using a normal serum in place of the serum to be tested. Both tubes are allowed to incubate for 15 minutes and then examined by means of smear preparations on slides spread and stained in the usual way. The degree of phagocytosis is then determined in each by counting a consecutive series of fifty leucocytes and finding the average number of bacteria ingested per leucocyte. This number for the serum to be tested is divided by the number obtained with the normal serum and the result regarded as the opsonic index of the serum in question.

VACCINE. A vaccine is any chemical or bio-chemical substance which when introduced into the organism causes there an elaboration of protective substances.

PREPARATION. The technique of preparing a vaccine for a staphylococcus infection say from a case of acne is as follows: The material for cultural purposes is obtained by puncturing the lesion with a sterilized needle, after washing the cutaneous surface with alcohol and ether. The pus expressed is transferred by the aid of a platinum loop to a plain agar slant, care being taken to ensure an even distribution of the material over the entire surface. This may best be

effected by employing several loopfuls of the water of condensation. In order to secure the highest efficiency it is desirable that the vaccines be prepared from the original cultures or from the first transplant.

After incubation for from twelve to eighteen hours the growth, if in pure culture, is washed from the surface of the slant with 6 c. c. of 0.85 per cent solution, and decanted into a sterile test tube. The tube is then drawn out and sealed in the blowpipe flame and the contents agitated for ten minutes to ensure an even emulsion for standardizing purposes, is expelled, and the tube is resealed and immersed in the water-bath for one hour at 60 degrees C. Finally a control culture is made and placed in the thermostat for twenty-four hours at the end of which time, if negative, the vaccine may be diluted for use.

STANDARDIZING. Into a long narrow pipette fitted with a rubber teat and upon which a volume has been marked with a blue pencil, equal volumes of finger blood and the emulsion withdrawn before devitalization are aspirated, together with one or more volumes of 0.85 per cent saline solution as a diluent. The contents of the pipette are then expelled upon a slide, thoroughly mixed by repeated aspiration, and films drawn. The latter are then stained by Leishmann's or Wright's blood stain and 500 red cells counted, noting at the same time the number of cocci present in the different fields. By a comparison of the two the number of

cocci per cubic millimeter may be readily determined. Thus if in counting 500 red cells 500 cocci are encountered the vaccine contains 5,000,000 cocci per cubic millimeter or 5,000,000,000 per cubic centimeter.

DILUTING AND LYSOLIZING. For diluted vaccine 50 c. c. amber-glass bottles are employed. These bottles are filled with 50 c. c. of 0.85 per cent saline solution, plugged with cotton-wool, and autoclaved. To continue our example of a vaccine standardized at 5,000,000,000 per cubic centimeter: after determining the cubic contents of the vaccine tube (or comparing it with a tube of equal size filled to the same level with water and measured) 5 c. c. of the contents of the bottle is poured into a cubic centimeter graduate, and replaced by an equal quantity of the concentrated vaccine. We thus have an emulsion 1 c. c. of which contains 500,000,000 staphylococci. We next add 0.25 per cent. of pure lysol that is 2.5 milligrams per cubic centimeter. Finally a sterilized rubber cap is drawn over the neck of the bottle, and the mouth of the bottle immersed to the shoulder in hot paraffin.

OPSONIC DIAGNOSIS. Wright and his co-workers have demonstrated that in disease due to either staphylococcus, streptococcus, colon bacillus or to other organisms, as well as the tubercle bacillus, whether the disease be localized as in acne or sinus infection or whether the infection occurs systemically in the blood, there exists a lowered opsonic index

for the particular organism in question and for none other. That is, in case of acne due to one of the staphylococcus group of organisms the index for the staphylococcus and for the staphylococcus alone is lowered while the index for the streptococcus and the tubercle bacillus remains unaltered. This specificity of opsonin is made use of by Wright and others in establishing a diagnosis in obscure conditions. They believe that the organism showing a lowered index is the organism etiologically concerned.

PRINCIPLES. Certain broad principles in the use of vaccines which obtain in the use of all vaccines, whether staphylococcus vaccine or tuberculin, will now be considered. Following the inoculation of a therapeutic dose of vaccine there occurs in the body fluids, as has been pointed out by Wright, Douglas, Hektoen and others, a fall in the opsonic-index, negative phase, which probably corresponds to the period of anchoring by the cell receptors of the haptin substances of the vaccine. Haptin is the name applied by Ehrlich to those substances capable of stimulating the body cells to produce antibodies. In the discussion of receptors on page ten the word toxin was used that the illustration might appear more clear. In the production of antitoxin the toxin molecule does enter into the relation with the cell as there stated, but in considering vaccines this does not hold, its place

as a stimulant being taken by the vaccine or haptin. When these receptors or antibodies are set free into the body fluids an increased antibody content would naturally follow which Wright designates as the positive phase with elevated opsonic-index. In the natural course of events many of the antibodies or opsonins fulfill their purpose and unite with the invading organism preparing it for ingestion by the phagocyte. It would therefore follow that the total opsonic content would be lowered but not to the original low point. This Wright calls a higher base line.

The result to be looked for, then, in exhibiting vaccines is to stimulate the body cells in such a way as to call forth the largest amount of antibody or opsonin the cells are capable of manufacturing. Wright holds that this may be done by inoculating the appropriate dose of vaccine during the positive phase only and at intervals of four to five days. Wright teaches that too frequent and too large doses of vaccine inhibit the machinery of immunization or the ability of the cells to throw off receptors, and he shows by numerous opsonic estimations that this is the case.

In the treatment of localized infections such as sinuses and carbuncles, Wright has shown that, while the blood itself may contain a high content of opsonin, the diseased local areas, owing to the inflammatory nature of the process, may be relatively poor in opsonin.

Therefore, in all cases of localized infection attention should be paid to the local condition and proper measures for increasing the opsonic content locally should be instituted in all cases. The use of the Finsen rays increases the flow of blood to a localized infected area, like lupus. If the opsonic index of the blood is raised beforehand, the lymph brought in contact with the organisms is more efficacious than it could possibly have been before. Heat applied to an inflamed area acts in the same way. Irrigation of sinuses and the application to carbuncles and boils of citrated salt solution promotes healing because the sodium citrate prevents coagulation of the blood which, if occurring, would plug up the lymph channels; sodium chloride promotes the flow of lymph by osmosis. Bier's hyperaemia, by increasing the flow of lymph and blood through diseased areas, brings fresh lymph of higher opsonic content to the part and therefore aids in recovery.

ACNE, FURUNCULOSIS AND CARBUNCLE. Much of the early work on vaccines was done on the simpler infections, acne, furunculosis and carbuncle and gave very gratifying results. While it can not be said that these infections are to-day treated with absolute success, it may however be stated that the results are in nearly all instances commensurate with the understanding of the individual using the vaccine. As in the treatment of all bacterial infections success in great

measure depends upon carefully determining the type of infecting organism present and preparing the vaccine directly from it. Care also must be exercised in all cases that the infection is a single one and not mixed. This may be determined by taking cultures two or three weeks after treatment has been begun when it will be found, if a mixed infection exists, that the original organism will not overgrow the other. The latter may then be recovered for therapeutic use.

In the great majority of the acne cases the staphylococcus will prove sufficient to effect a cure. In the few proving resistant to this organism or in cases in which no organism can be recovered on the ordinary media the acne bacillus can be isolated on special media. The vaccine made from this acne bacillus will give the desired result. Furthermore, and this applies to vaccine problems at large, cognizance must be taken of the fact that infections remote and different in character from the particular one in question may through growth so influence the machinery of immunization that a cure may not be obtained until the focus or foci shall receive appropriate treatment. To illustrate, one case of acne failed to heal until a chronic nasal infection had received specific attention. A second case proving equally resistant yielded readily when a chronically infected bladder received the proper treatment.

ANTITYPHOID INOCULATION. Antityphoid inocula-

tion with vaccines has been thoroughly studied since 1896 when Pfeiffer did the pioneer work in it. Wright placed the method on a firm basis by his inoculations in the British army, both in India and during the Boer War. Since then there have been many contributions to the subject, especially by Leishman, whose work has helped greatly to bring the subject up to date, as has also the work of Major Russell of the United States Army.

METHOD OF ADMINISTRATION. The Royal Commission, appointed in October, 1904, found that an interval of about ten days should separate the doses. The first dose consists of 500 millions to 1,000 millions, and the second from 1,000 millions to 1,500 millions. In the United States Army a third dose ten days later is given of the same amount as the second. The injections should be made in the outer side of the arm or in the abdominal muscle. Reactions vary in degree from moderate local redness at the site of inoculation accompanied by headache and malaise, to a large indurated area with swelling of the axillary glands and severe general reaction (headache, backache, nausea, vomiting, herpes labialis and rarely albuminuria and loss of weight. The entire reaction is over in 48 hours. Following the first inoculation there is a temporary decline in the antibodies of the blood which later steadily rise reaching their maximum on about the tenth day. The antibodies participating in this reaction are the agglu-

tinins, bactericidins, bacteriolysins, and opsonins. The increase of the opsonins is marked reaching 2 to 2.5 following the first inoculation and after the second injection 3 to 5.5.

The duration of immunity produced by preventive inoculations has been variously estimated at from two to six years. In many cases the immunity probably lasts for life, although of this conjecture no definite proof exists.

As to the value of antityphoid inoculations against paratyphoid infection there appears to be a difference of opinion. Clark and Simonds find that "opsonins arising in typhoid are capable of stimulating phagocytosis of paratyphoid bacilli; while Leishman and his co-workers were unable to verify their observations.

Statistics to the present time certainly indicate that in antityphoid inoculations we have a most valuable asset in combating an epidemic and that they should be used in the following classes of persons: all nurses, ward attendants, hospital corps men, red cross assistants, physicians, medical men, soldiers; also all persons who contemplate a journey into a section where typhoid is known to exist or is suspected of existing. Also the inoculations should be done generally in districts suffering from an epidemic and especially in families where a case exists. Investigations have established that about four per cent of convalescent typhoid cases become chronic "typhoid carriers" dis-

seminating the infection more or less constantly by the urine and feces for periods of years. Practically all these cases are curable with antityphoid inoculations.

COMMON COLDS-NASAL CATARRH-HAY FEVER. The common cold may be caused by one or more of several organisms commonly found in the tonsils and nasopharynx: such as the bacillus of Friedlander, bacillus septus, micrococcus catarrhalis or pneumococcus. Lowered resistance on the part of the tissues, or increased virulence on the part of the organism, or both, excites the organism to activity and a cold results. A cold may be aborted by the inoculation of the proper vaccine, and furthermore those individuals subject to recurring attacks of colds may obtain relief by being immunized against the offending organism.

The treatment of chronic nasal catarrh is more tedious as in these cases much difficulty may arise in obtaining the specific organism in pure culture. When invasion of the sinuses occurs free drainage must be secured before a cure can be expected. It is still possible, however, even in these cases, to protect the patient from recurring attacks of cold by properly immunizing them against the exciting organism. Many cases of chronic bronchitis resistant to ordinary methods are favorably influenced by vaccine treatment.

Carmalt Jones reports 50 cases of asthma in which he isolated a short Gram negative bacillus. Allen

failed to find a constant organism as the cause of this disease and reports indifferent results.

In five cases of hay fever which reported for treatment last October the micrococcus catarrhalis was present in all in the nasal secretion and vaccines gave marked relief.

Bordet describes a cocco-bacillus in pertussis, Gram negative, non-motile, growing in three days on blood agar. Freeman has inoculated about 100 children suffering from the disease with encouraging results.

VACCINE THERAPY AS AN ADJUNCT TO SURGERY. Surgery and vaccine therapy must go hand in hand. Surgery has need of vaccines in preventing and healing infections. Vaccine Therapy is dependent upon surgery to open localized foci and establish drainage.

Deaver, DaCosta, Pfeiffer and others agree that vaccines are efficient in only early cases of streptococcus septicemia. Staphylococcus septicemia yields readily to vaccine treatment with autogenous vaccines in all stages. Septic intoxications, without demonstrated blood invasion in a majority of cases display general and local improvement under the use of vaccines. Localized and persistent suppurating lesions are markedly benefited by vaccines.

Preventive inoculations in surgery give as brilliant results as in medical diseases. We know that the pathogenic bacteria most to be feared in the intestinal canal are streptococcus and colon, rarely pneumococ-

cus. It is, then, rational to give an immunizing dose of one or more of these bacteria 3 or 4 days before an operation of election upon the abdominal cavity when the intestine may be injured or opened. By the same process of reasoning, if a culture be taken from the genito-urinary tract at a sufficient interval before operation to allow the making of a vaccine from the organisms found there, and the patient be immunized by this means, one grave danger from the operation, viz.: sepsis, may be averted.

Our series of cases shows two striking examples. (1) A case of resection of the lower end of the sigmoid for a malignant stricture received an immunizing dose of combined colon and streptococcus vaccine 3 days before operation. There was perforce much damage done the peritoneum and feces were spilled in the abdominal cavity. The convalescence was uneventful, the temperature reaching its highest point, 100° , 36 hours after operation. An almost exactly similar case, which did not receive vaccine, died from streptococcus peritonitis on the third day following operation. (2) After the removal of an hypertrophied prostate by the suprapubic route the bladder was sewed up tight and drained by a catheter through a stab wound in the perineum. The patient was immunized by an antogenous colon vaccine three days before operation. There was no suprapubic leakage either before or after the removal of the perineal drain on the sixth day following operation.

De Forrest Willard and Thomas of Philadelphia report their experience in the use of vaccines in bone and joint disease as follows: "We have now had two years of experience in the treatment by bacterins of tuberculous bone and joint diseases, complicated by mixed pyogenic infections. The feature of the treatment consists in the alternation of bacterin and tuberculin inoculations in the mixed suppurative type of the disease, as spinal caries, tuberculous hip-joint disease, etc. We do not contend that bacterin therapy is a "cure all," nor that when indications for surgical intervention exist, they can be disregarded and active immunization substituted. However the accessory employment of bacterin and tuberculin in certain cases stimulates the tissue cells of the organism to the production of specific antibodies to assist the bodily defenses in antagonizing and combating the given infections. Bacterins, particularly tuberculin, are invaluable aids in competent hands, and when so treated such patients do better than those treated without bacterins; their detention in the hospital is shortened, and complications, if they occur, are fewer and less severe. Studious observations of the clinical symptomatology have always sufficed to control the treatment, the opsonic index proving impractical."

GNOCOCCUS INFECTIONS. In gonococcus infections the value of vaccines seems to be still 'sub-judice.' O'Neil, in a complete review of the subject early in

1910 comes to the conclusion that gonorrheal rheumatism, gonorrhea of the adnexa, both male and female and even gonorrheal septicemia are favorably influenced by vaccines. He further states that even the autogenous vaccines, without other (i. e. mechanical) treatment, are of no avail in the urethritis cases. We do not expect vaccines to have a curative action on enclosed foci. There must be drainage. The urethra is plentifully supplied with mucus glands, large and small, through its length, and these glands offer sufficient opportunity for the gonococci to pocket.

Within the past year Mark and other observers have reported urethritis cases cured in much shortened time by using autogenous vaccines and proper mechanical treatment in conjunction. In our own series of cases we find that we may expect cure within one week in 80 per cent of the cases by using a stock gonococcus vaccine and the proper mechanical treatment if seen within twenty-four hours of the onset of symptoms. In those cases coming to us after twenty-four hours and under seventy-two hours after onset, the percentage of cures within one week is less than 40 per cent. After the third day the vaccines seems only to lessen the chordee and counteract the physical depression of the patient.

We use stock vaccine only until such times as the autogenous vaccine can be prepared.

DISEASES OF THE BLADDER AND PROSTATE. The

role which bacteria play in diseases of the urinary bladder needs no comment. The use of vaccines in the treatment of bladder diseases is full of possibilities and promise.

Perhaps the simplest form of bladder disturbance, especially in the female, is frequency of urination. This troublesome affliction is almost invariably due to bacterial invasion either by the colon organism or by the staphylococcus. In either instance relief may be obtained by exhibiting the appropriate vaccine.

Deeper seated infections with little or much pus in the urine may in most instances be benefited if not cured by prolonged local and vaccine treatment, the offending organism in most cases being the bacillus coli communis, it must be constantly born in mind in all bladder infections that the tubercle bacillus is not an infrequent invader of the bladder and it should therefore receive especial consideration in these cases.

In prostatic hypertrophy the urine in all cases examined has shown the presence of bacteria. In all but one case the organism was the coli communis. In one case the urine showed a colon growth while bacteriological examination of the depths of the prostate removed at operation revealed only a coccus. In one case repeated examinations showed the presence of a coccus only. The following case illustrates the use of vaccines in this disease. In March, 1910, after twenty years of bladder pain, frequency and discomfort, a patient of

72 years old was unable to pass any urine. A catheter was tied in, which, after a short time, he was unable to stand. There was loss of weight, marked exhaustion, and edema of feet, abdomen and scrotum, 16 ounces of dirty foul residual urine. On June 24th an autogenous vaccine was given; in two weeks' time the residual urine amounted to 4 ounces; the edema and exhaustion were gone and the patient was greatly improved. By the middle of August the patient returned to his home free from pain and discomfort resorting to the use of the catheter about once a week.

TUBERCULOSIS. Ten years after Robert Koch in 1890 announced that he had discovered in tuberculin a cure for tuberculosis, the tuberculin therapy had passed through the period of "tuberculin delirium" and had arrived at the age of "tuberculin terror" and he who used tuberculin at this period was considered a criminal. A few men (Trudeau, Goetsch, Klebs, Petruschy, Von Ruck) continued the use of tuberculin, and to them is due the fact that the period of "tuberculin renaissance," which began a few years ago came to pass. Much credit is however due to Wright and Denys in establishing the dose within sane and safe limits. Wright applies the same opsonic method already described in connection with other infections as a means of determining the dose and goes to great length to point out the fact that small doses stimulate the machinery of immunization more effectually than large doses.

The crucial point in the tuberculin treatment is the selection of the dose and the interval. The variety of tuberculin used is of much less importance. In the treatment of all tuberculosis cases especially those of the lung and kidney great care must be used to avoid systemic reactions. Systemic reactions are shown by an increase in temperature and pulse rate, by slight headache, by malaise and physical depression, by fatigue, by a tired feeling, by insomnia, by somnolence, by restlessness, by nervousness, by pain in back or limbs, by indigestion or nausea, and by the aggravation of any existing symptom. The occurrence of any of the above symptoms may be due to factors other than tuberculin, but it is always safer in case of doubt to omit the next dose or at least to decrease it. Symptoms of improvement in the local condition are to be looked for after the third or fourth dose while symptoms referable to the depressing effects of the bacterial toxin itself such as a tired and exhausted feeling and sense of ill being should show almost immediate response. In deciding upon the initial dose cognizance should be taken of the patient's weight, age, activity of the disease process, occupation, and duration of illness. And it would follow that the patient actively employed with considerable physical depression and with but a moderately active lesion should receive a smaller dose than the individual of quiet habits and with a fairly active process. Furthermore the time at which

the inoculation is given should be considered in determining the size of the dose inasmuch as the individual tired from a day's work and without the proper sustenance reacts more easily than the patient well fed and beginning the day's work. Care should also be exercised in inoculating women during the menstrual period for at such a time severe reactions may be caused by a relatively small dose. For an initial dose, in the average case I use $1/50000$ m. g. of B. E. Human and of the Bovine T. R., $1/70000$ m. g. The doses may as a rule be rapidly increased but I have never given a larger dose than $1/1000$ m. g. of the former and $1/5000$ m. g. of the latter.

It should be the object of the treatment to gradually increase the dose, at the same time keeping the patient in a good physical condition. From this it follows that to increase successive doses in logarithmic progression without regard to the patient's condition, as is advocated by some, is unscientific and only invites disaster.

The dose is gradually but progressively increased depending entirely upon the patient's condition. Should the patient show improvement in weight and general condition, then it is safe to infer that the dose can be gradually increased. With those cases progressing intermittently as it were, improving one week and declining the next, the dose is not suited to the exigencies of the case, by which I mean some untoward influ-

ence is operating. To these patients, if one is unable to control them, it is best to give a comparatively small dose and err on the safe side. Patients will complain that the effects of the dose wears off before the next inoculation, which indicates that the dose was insufficient or that the interval between the doses was too long. It will also be observed that patients will progress to a certain point and then remain uninfluenced by an increase or a diminution of the dose or by a change in the tuberculin. These patients should be given a rest from treatment of from two to three weeks. No patient in my experience is intolerant to tubereulin: failure to obtain results has not been due to error in indication but to error in judgment and technique.

INDICATIONS FOR TUBERCULIN. Tubereulin should be used in all cases of incipient tuberculosis with but moderate temperature elevation, 99.5-100. It is safe in fact, providing one is familiar with the use of tuberculin, to exhibit it in practically all tuberculous conditions. From this one need not infer that it will prove curative in all tuberculous conditions. For in those cases with a daily temperature of 101.5 or more the dose would necessarily be of such a small quantum that the immunizing effect would be practically nil. In pulmonary cases one should be guided by the weight, general condition, temperature and pulse rather than by the stage of lesion. Should emaciation,

moderate elevation of temperature or rapid pulse exist with but moderately active process the patient will do better without than with tuberculin. On the other hand a patient in comparatively good general condition even with a fairly advanced lesion may do well on tuberculin.

As in all infectious diseases, so in tuberculosis, a period of quiescence or incubation must precede the advent of a recognizable lesion. This period may vary in duration from a few weeks to several months. Not infrequently during this time the question arises as to whether or not the patient has tuberculosis. This is the ideal time to begin treatment with tuberculin. Patients of this class respond promptly and surely leaving no question in the observer's mind as to the nature of the poison which was causing the depression.

SECONDARY INVADERS. At present there is great divergence of opinion as to the influence of secondary organisms on the course of pulmonary tuberculosis. It is, perhaps, a fact that many of these secondary organisms are of low vitality and non-virulent, but it is just as possible for such patients to rid themselves of these as of local infections, such as acne, furunculosis, both such frequent afflictions of the tuberculous. Examination of sputa, culturally and by smear, from a large number of cases shows the presence of streptococcus pyogenes in most cases and less frequently the pneu-

mococcus (Fraenkel) the staphylococcus and the micrococcus catarrhalis.

Ravenel and Irwin examined all the organs in fifty-six cases autopsied and found that the bacillus coli communis was present in the kidney nineteen times and in the liver twenty-nine times. Webb published the results in fifty cases inoculated with homologous vaccines prepared from the mixed organisms which are best summed up as follows:

1. In no case has a patient been harmed.
2. Many patients have had exacerbations more rarely.
3. Expectoration in nearly all cases has been lessened; nocturnal coughs have frequently been eliminated.
4. In some cases a chronic catarrhal hoarseness has entirely disappeared.
5. Concomitant pus affections have cleared away, such as suppuration of ears, staphylococic acne, and sycosis.
6. When these vaccines have been combined with small doses of Koch's new tuberculin, spreading infiltrations have been averted and cleared up.
7. In a case which displayed tubercle bacillus, streptococcus, pneumococcus, staphylococcus and Micrococcus catarrhalis, the latter was entirely eliminated

by appropriate vaccine, and the amount of sputum was reduced from four ounces to less than one ounce daily.

8. Evacuations of four to six ounces of sputum daily from cavities have, in several cases, been reduced to less than one ounce. In conclusion, Webb puts forth the earnest plea that these potent remedies be used early, while the machinery of immunization is yet unworn, and that they be added to the tuberculin treatment so well advocated by Trudeau and Wright. Then the ranks of the advanced tuberculous will be lessened.

CASE REPORT. Case of T., twenty one years old. Commenced treatment May 22, 1909. Had had four hemorrhages; temperature 101, pulse 116, moderate cough; small amount of sputum; no tubercle bacilli found; night sweats; exhaustion; loss of weight; no gastric disturbance; chest without recognizable lesion. Von Pirquet skin test positive. Treatment consisted in rest, diet, tuberculin and Human B. E. By June 16, 1909, patient showed improvement in strength, physical condition, weight; temperature normal, pulse 96. Tuberculin continued. In November, 1909, patient returned to work exercised unduly all night on one occasion and shortly afterwards fell sick as before. His condition grew progressively worse so that by January, 1910, there was a well marked consolidation extending downward from the clavicle on the right side to the third rib, temperature 102, pulse 120 — hemorrhages

increased sputum and exhaustion. At this time a streptococcus vaccine was prepared from sputum, which was given together with tuberculin. Unfortunately the patient was so situated that he could not obtain the advantages of rest and open air treatment but was obliged to dress daily and move about. By May 1, 1910, his temperature was normal and his general condition was greatly improved. To-day, April 1, 1911, the patient is well and strong. He has gained twenty pounds, and his chest is without discernible lesion. Tuberculin was given throughout the entire course of the disease. This is one of ten cases which I have either personally treated or have observed all of which are now practically cured.

IN UROGENITAL TUBERCULOSIS. The indications for the use of tuberculin has been summarized by Sanborn as follows: (1) In case of organs involved which cannot be extirpated, such as the bladder.

(2) In case of any organ in which tuberculosis is very early and in which disintegration has not taken place to any considerable extent.

(3) In case of tuberculosis of both kidneys where it is deemed unwise to operate either. (4) Post-operatively in case that it is apparent that all tuberculous tissue was not removed or where organs that were involved could not well be extirpated. (5) In any case where bladder involvement is present. (6) In any case where there is a suspicion that tuberculous

tissue has been left behind. These indications appear to be conservative and safe. They leave the surgeon free to exercise his art and seek only, as in all types of opsonic treatment, to aid nature in her effort to throw off disease. The results are encouraging.

Carmalt Jones reports the cases of renal tuberculosis treated in Wright's clinic. Of the cases treated two were considered cured, two better, two somewhat better and one dead. Care should be exercised in treating these cases inasmuch as an injection of an undue amount of tuberculin might, as in a case reported by Walker, set up a focal reaction in an existing lesion situated within the ureter and lead to marked untoward results. Jones reports the cases of tuberculous cystitis treated in Wright's clinic as follows: Two cases cured; 4 much better; 8 better, meaning either some relief from pain or frequency of micturition. One case was no better, one worse and one unknown. There were relapses in five cases. In thirteen cases there was secondary colon infection. In ten of the successful cases, the initial dose was less than 1-15,000, but often 1-25,000. After a time it was raised gradually to 1-4,000. Serious results may follow large initial doses. The treatment of successful cases averaged one year and two months. Five or six cases were treated six months or less. Jones reports the following results in cases of tuberculosis of the testicle treated in Wright's clinic; three cases were cured; two much better; and two doubtful as to the result.

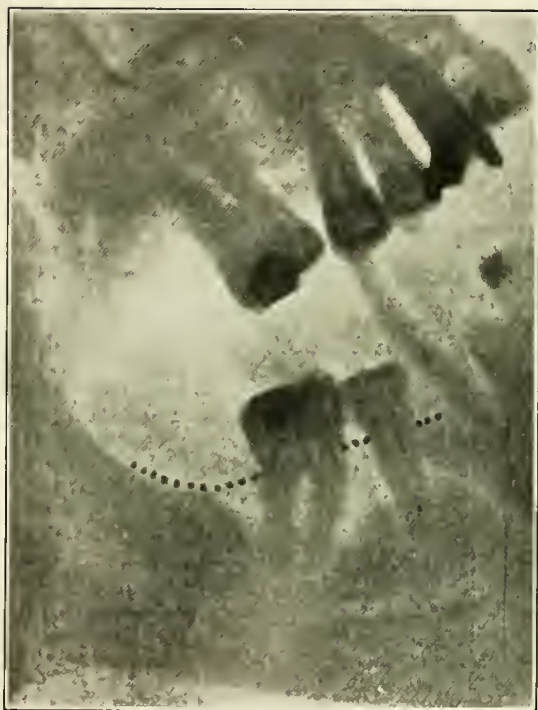
TUBERCULOSIS OF THE CERVICAL AND OTHER GLANDS. In the treatment of tuberculosis of the lymph glands with tuberculin the problem while at times simple at other times becomes difficult. Relatively small glands almost invariably do well under tuberculin treatment. The larger the gland other things being equal unless softening occurs the more difficult the treatment. Those patients obviously operable, with large multiple glands showing loss of weight and physical depression should receive a course of tuberculin before and after operation. It is impossible to say beforehand how a given case will react to the treatment because one is unable to judge either the existing condition in the gland or the state of the patient's immunizing power.

RHEUMATISM. Recently the leaning of most writers has been to regard the cause of most chronic joint disorders which take their origin in the capsule and periarticular tissues as due to bacteria either within the joint or tissues or to a toxin produced by organisms in some other part of the body. The predilection of certain bacterial toxins for certain tissues is a well recognized bi-ological fact, and it has further been shown that the injurious action of bacterial toxins may operate over a long period of time on the particular tissue to which it unites itself without markedly depressing the economy at large. With the chronic rheumatoid affections it would

appear then that the very nature and chronicity of the disease should point to an etiological organism or toxin possessing selective features for the tissues involved and of only moderate virulence. Goadby in The Hunterian Lecture delivered March 6, 1911, at The Royal College of surgeons of England brought forth convincing proof that such an organism existed in practically all cases of rheumatoid disease examined by him. The toxin of the strepto-bacillus isolated by Goadby unquestionably has a selective affinity for periosteal and ostial tissues as is shown clinically and experimentally on animals.

FREQUENCY OF INFECTION. In 1908 Lindsay reported 172 cases of rheumatoid arthritis in which particular inquiry was made for infective foci. In 88 of these cases an infective focus was discovered.

Lambert in the same year reports that of 190 cases 141 (76 per cent) had badly decayed teeth or the teeth had dropped out and 49 showed teeth in fairly good condition. Llewellyn Jones in discussing diagnosis says "strong presumptive evidence of infectious arthritis may be drawn from the presence of any local source of infection, such as pyorrhea alveolaris, otorrhoea and so forth." MacNamara states that he had traced many cases to the chronic poisoning of septic teeth. Luff, Spender, Fayerweather and many others consider the gastro-intestinal tract as the origin of infection, while Hunter, Goadby and others have demon-



SHOWING THE DESTRUCTION OF TISSUE WHICH HAS TAKEN PLACE IN
THE LOWER JAW. DOTTED LINE INDICATES THE
NORMAL LINE OF BONE.

FROM MR. GOADBY'S ARTICLE, LANCET MARCH 11, 1911.

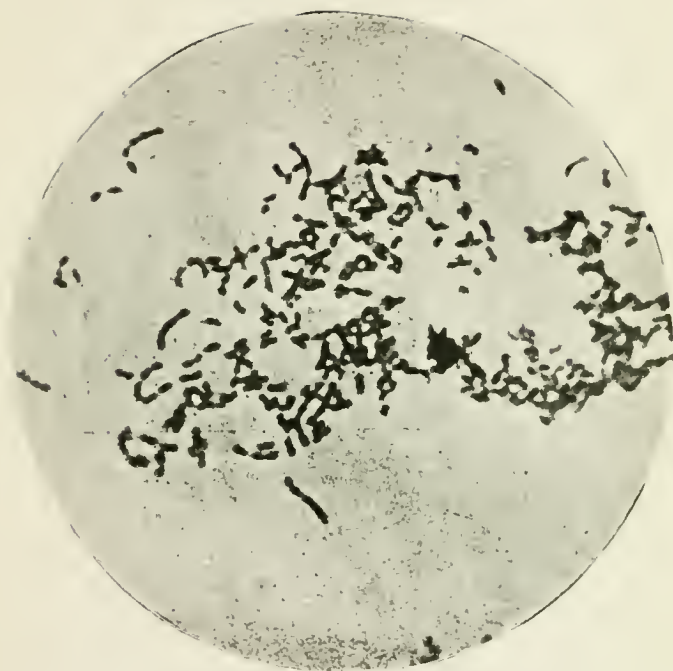
strated the relationship of oral sepsis to gastro-intestinal affection. In twenty-five cases of rheumatoid arthritis observed by the writer all had or had had pyorrheo alveolaris.

The organism isolated by Goadby is not unlike the organism which the writer has used during the past eighteen months in the treatment of rheumatoid cases. Goadby describes his organism when grown freely as a strepto-bacillus not unlike Duerey's bacillus but in colonies taken direct from the plates on first plating a diplo-bacillary form is common. The organism used by the writer was the diplo-bacillus form and all vaccines were prepared from this organism. It was noted however that many of the original cultures planted in bouillon at the end of 48 hours yielded a strepto-bacillus. Goadby reports that the younger cultures were stained by Gram's while the older ones in many instances were Gram negatives. He further states that in the older cultures and some of the younger cultures, where the organism is not growing freely, there are certain curious forms which may or may not be regarded as involution forms. He mentions three types: 1. Large oval, swollen forms two to three in width. 2. Large coccil forms, irregular in shape and associated in clusters. 3. Oval elongated, and shuttle shaped forms occurring frequently in the length of the chain. The organism grows readily on gelatin agar but dies out quickly unless subcultured within a few days. There

appears to be no definite regularity in the carbohydrate fermentation. Litmus milk is rendered acid, and in the majority of cases coagulated. On gelatin agar the colonies are isolated averaging about two millimeters in diameter. The colonies are greyish white and are of a flaky consistency when removed with the wire.

Goadby, following the suggestion of Mr. Clement Lucas, was able by direct inoculation of rabbits' joints, to produce in 18 rabbits, symptoms indistinguishable from arthritis deformans. Goadby describes to great length these joints. The description of one is as follows: "The head of the tibia and the lower end of the femur on the outer side both show alterations in the synovial structures. The joint itself is typically that of arthritis deformans, the photograph being taken nine months after inoculation only one injection having been made. The alteration of the head of the tibia and the thinning of the tuberosity are definitely shown." There appears also from the photograph to be some sclerosis in the head of the tibia and the lower end of the femur, recalling to some extent the rarefaction associated with sclerosis shown in the earlier photographs of the local disease of the jaw.

Goadby divides his cases into three groups assigning to group A those cases with definite arthritis. Definite arthritis of one or more joints, with pain, swelling, limitation of movement, and with or without wasting of one or more muscles in the neighborhood of the



SHOWING THE DIPLO-BACILLUS FORM OF THE STREPTO BACILLUS.
FROM MR. GOADBY'S ARTICLE, LANCET MARCH 11, 1911.

joint. Swelling of tendons or tendon sheaths in the neighborhood of joint or elsewhere. Muscular pains, diffuse and irregular in distribution and origin. Neuralgia of trigeminal type. Anaemia. Group B. No definite arthritis; inflammation, or swelling of tendon sheath or tendon. Diffuse muscular pains, irregular in distribution and origin. Occasional swelling of joints or tendons, clearing up and leaving no objective symptoms. Palpitation, with irregularity of heart action. Tachycardia. Neuralgia, trigeminal type. Sciatic pain not definitely referred to the sciatic nerve, but diffuse and referred. Gastric and intestinal symptoms.

Group C. Occasional swelling and tenderness in joints or tendons, rapidly clearing up and leaving no objective symptoms. Irregular muscular pains, occasionally associated with stiffness. Tingling, or "pins-and-needles" sensation in the extremities. Local asphyxias or other vaso-motor phenomena. Intermittent lumbago. Occasional trigeminal neuralgia.

These three types gave respectively 25, 16, and 8 cases. Of the total number of cases with a history of rheumatic symptoms, 15 were males and 34 females.

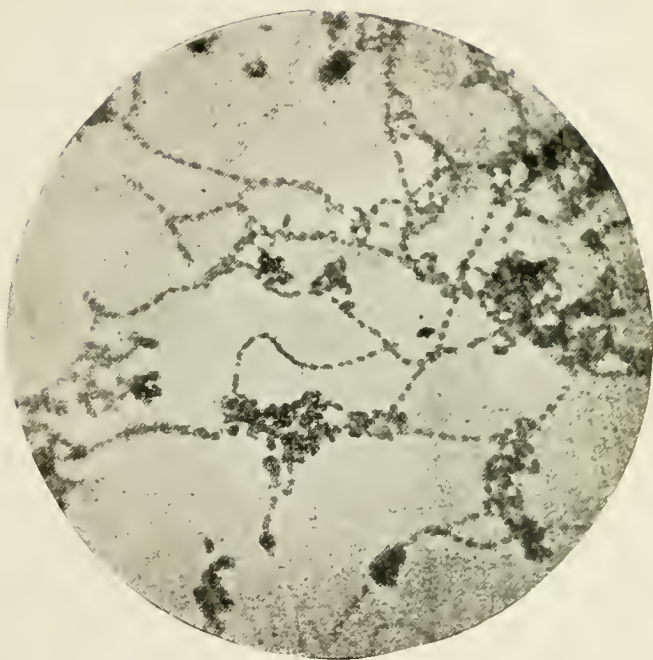
VACCINE TREATMENT: Of the 49 cases, 45 received autogenous vaccines made from the streptobacillus malar. The initial dose was about 10,000,000 which was in most instances followed by an exacerbation of the joint symptoms. The dose was gradually increased to

200,000,000 and was given at seven to ten days intervals. Of the 21 cases belonging to Group A, eleven were cured, seven relieved, two unimproved, four still under treatment. Of the sixteen cases of group B, seven were cured, seven relieved, two unimproved, two still under treatment. Of the eight cases of group C, five were cured and three were relieved.

Goadby does not claim that his contribution to the study of arthritis deformans establishes a specific organism as the etiological factor in all cases of rheumatoid arthritis, infective fibrositis, muscular rheumatism, etc., but that in diseases of the jaws, especially rarefying alveolar osteitis, a streptobacillus is present, pure cultivations of which inoculated into or around the knee joints of rabbits have produced symptoms similar to and indistinguishable from arthritis deformans; that in such disease of the mouth and jaws the treatment of the disease locally and by means of autogenous vaccine prepared from the streptobacillus has been associated with amelioration and disappearance of the arthritis symptoms in a greater number of instances than can be ascribed to fortuitous coincidence.

CONCLUSIONS. The writer as may be seen from this paper is a firm believer in vaccine therapy. He realizes only too keenly its shortcomings but he feels that the under-lying principle is sound and well founded.

While insufficient evidence is now at hand to war-



STREPTO BACILLUS.
FROM MR. GOADBY'S ARTICLE, LANCET MARCH 11, 1911.

rant a distinct change in the quantum of dose as set forth by Wright the writer feels in view of the work already done on antityphoid immunization and of the results accomplished by Ehrlich in his treatment of syphilis with Salvarsan and of the more recent work of Schaffer published in the *Therapeutic Gazette* for April 15, 1911, that in the chronic infections at least, the initial dose must be many times larger than the one employed at the present.

Statistics have been purposely omitted for the reason that most of them on this particular subject appeared to be unreliable and misleading.

With but few exceptions the subjects treated upon in the text have dealt with immunizing problems with which almost daily contact have made the writer familiar.

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